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DIAZINON

DRAFT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

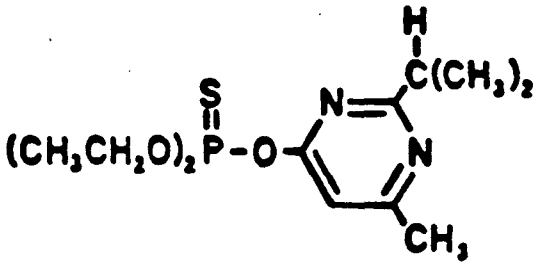
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 333-41-5

Structural Formula



0,0-Diethyl-0-(6-methyl-2-(1-methylethyl)-4-pyrimidinyl)ester

Synonyms

- Antigal; AG-500; Basudin; Bazudin; Ciazinon; Ducutox; Dassitox; Dazzel; Dianon; Diater; Diaterr-Fos; Diazajet; Diazide; Diazitol; Diazol; Dicid; Dimpylat; Dizinon; Dyzol; Exodin; Flytrol; Galesan; Kayazinon; Necidol/Nucidol; R-Fos; Spectacide; Spectracide (Meister, 1985).

Uses

- Soil insecticide; insect control in fruit, vegetables, tobacco, forage, field crops, range, pasture, grasslands and ornamentals; nematocide in turf; seed treatment and fly control (Meister, 1985).

Properties (Meister, 1983; Windholz et al., 1983)

Chemical Formula	$C_{12}H_{21}O_3N_2SP$
Molecular Weight	304.36
Physical State (25°C)	Colorless oil
Boiling Point	83 to 84°C (0.002 mm Hg)
Melting Point	--
Density	--
Vapor Pressure (20°C)	1.4×10^{-4}
Water Solubility (20°C)	40 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Diazinon has been found in 7,230 of 23,227 surface water samples analyzed and in 115 of 3,339 ground water samples (STORET, 1987). Samples were collected at 3,527 surface water locations and 2,552 ground water locations, and diazinon was found in 46 states. The 85th percentile of all nonzero samples was 0.20 ug/L in surface water and 0.25 ug/L in ground water sources. The maximum concentration found was 33,400 ug/L in surface water and 84 ug/L in ground water.

Environmental Fate

- ^{14}C-Diazinon (99% pure), at 7 or 51 ppm on sandy loam soil, degraded with a half-life of 37.4 hours after exposure to natural light (Blair, 1985). The degradate, oxypyrimidine, was detected at a maximum concentration of 19.60% (13.5 hours) of applied material when exposed to natural sunlight. After 35.5 hours (37.4 hours is the half-life) of sunlight exposure, 20.7% of the radiolabeled material was in soil-bound residues (some of which contained oxypyrimidine), 24.4% was oxypyrimidine and 39.7% diazinon. Losses of 7% were attributed to volatilization of diazinon and degradates (of which 0.5% was carbon dioxide). The total ^{14}C-radioactive material balance was 87-89% at the 0 hour and 84% at all other experimental points.

- ^{14}C-Diazinon (99% pure) degraded in sandy loam soil with a half-life of 17.3 hours when exposed to natural sunlight (Martinson, 1985). The degradate, oxypyrimidine, was detected at maximum concentrations of 23.72% (32.6 hours) of applied after exposure to natural sunlight. The degradate 2-(1'-hydroxy-1'-methyl)ethyl-4-methyl-6-hydroxypyrimidine was present after 8 hours of natural sunlight exposure at 3.6% of the applied material but was not present in the non-exposed samples. An unidentified degradate resulting from non-photolytic degradation (since it was also present in non-exposed samples), accounted for about 7% of the applied material under sunlight.

- In a Swiss sandy loam soil at 75% of field capacity and 25°C, ring-labeled ^{14}C-diazinon (97% pure) applied at 10 ppm rapidly degraded to 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMHP) with a half-life of less than one month. Within 14 days only 12.3% of the activity was found as the parent; 72.9% was identified as IMHP. Breakdown of IMHP was slower than that of diazinon and 49% of the applied radioactive material was in the form of IMHP after 84 days. After 166 days the amount of IMHP decreased to 4.7% of the applied material. Increased recoveries of $^{14}CO_2$ (55.6% after 166 days) and unextracted ^{14}C residues (15.1% after 166 days) corresponded to IMHP breakdown. No other major metabolites were found. Radioactivity in the H_2SO_4 and ethylene glycol traps was <1% of the applied ^{14}C throughout the study and material balance was generally above 80% of the applied material (Keller, 1981).

III. PHARMACOKINETICS

Absorption

- Mucke et al. (1970) reported that in both male and female rats, 69 to 80% of orally administered diazinon is excreted in the urine within 12 hours. This indicates that diazinon is well absorbed from the gastrointestinal tract.

Distribution

- The retention of diazinon labeled with ^{14}C in the pyrimidine ring and in the ethoxy groups was investigated in Wistar rats (Mucke et al., 1970). Doses of 0.1 mg/rat were administered by stomach tube daily for 10 days. Tissue levels 8 hours after the final dose were as follows: stomach and esophagus, 0.25%; small intestine, 0.65%; cecum/colon, 0.76%; liver, 0.16%; spleen, 0.01%; pancreas, 0.01%; kidney, 0.04%; lung, 0.02%; testes, 0.02%; muscle, 0.77% and fat, 0.23%.

- Chickens were fed diazinon at levels of 2, 20 or 200 ppm in their food for a period of 7 weeks (Mattson and Solga, 1965). Assuming that 1 ppm in the diet of chickens is equivalent to 0.125 mg/kg/day, this corresponds to doses of about 0.25, 2.5 or 25 mg/kg/day (Lehman, 1959). At the end of the feeding period, tissues from the animals fed 200 ppm (25 mg/kg/day) in the diet were analyzed for diazinon. There was no diazinon detected in fat, white or dark muscle, heart, kidney, liver, gizzard or eggs. The limit of sensitivity of the method was 0.05 ppm. There appeared to be no accumulation of diazinon in the body at 200 ppm (25 mg/kg/day) in the diet.

Metabolism

- The metabolism of diazinon ^{14}C-labeled in the pyrimidine ring was investigated in Wistar rats (200 g) after administration by stomach tube (Mucke et al., 1970). In addition to some unchanged diazinon, three major metabolites, all with the pyrimidine ring intact, were identified in the urine, and to a lesser degree in the feces. A fourth fraction containing polar materials was also found. The three main metabolites were the result of a split at the oxygen-phosphorus bond, with subsequent hydroxylation of the isopropyl side chain. There was no significant expiration of labeled carbon dioxide, further indicating that the pyrimidine nucleus remained intact.

- The metabolism of diazinon was investigated in vitro in rat liver microsomes obtained from adult male rats (Nakatsugawa et al., 1969). It was found that diazinon underwent a dual oxidative metabolism consisting of activation to diazoxon and degradation to diethyl phosphorothioic acid. The authors noted that they had observed similar pathways in studies with parathion and malathion, and these results emphasized the importance of microsomal oxidation in the degradation of organophosphate esters, indicating that many of the so-called phosphatase products or hydrolysis products may actually be oxidative metabolites.

Excretion

- The excretion of diazinon labeled with ^{14}C in the pyrimidine ring and in the ethoxy groups was investigated after administration by stomach tube to Wistar rats (Mucke et al., 1970). The diazinon was excreted rapidly by both male and female animals, and 50% of the administered dose was recovered within 12 hours. Of this, 69 to 80% was excreted in the urine, and 18 to 25% in the feces. There was negligible expiration of labeled carbon dioxide. There was no evidence of accumulation of diazinon in any tissue.

IV. HEALTH EFFECTS

- Diazinon is a reactive organophosphorus compound, and many of its toxic effects are similar to those produced by other substances of this class. Characteristic effects include inhibition of acetyl cholinesterase (ChE) and central nervous system (CNS) depression.

Humans

Short-term Exposure

- Weden et al. (1984) described a case report of diazinon poisoning in a 26-year-old man who deliberately ingested a preparation containing an unknown concentration of diazinon in an apparent suicide attempt. Upon admission to the hospital, the patient exhibited most of the usual symptoms of organophosphate poisoning, including muscarinic, nicotinic and CNS manifestations. During treatment and monitoring, it was noted that the urine output was very low and was dark and cloudy in appearance. By the second day, the urine was found to contain moderate amorphous crystals that could not be identified. With increased intravenous fluids, the urine output increased, but the crystaluria persisted and increased up to the 4th day, with a gradual decrease for the next 5 days, at which time the patient was discharged. Serum creatinine and urea nitrogen levels remained normal throughout this period. It was noted that this phenomenon may have been related to the specific pesticide formulation that had been ingested, but the authors suggested that renal function should be monitored more closely in persons with organophosphate poisoning.

- Two men reportedly developed "marked" inhibition of plasma cholinesterase following the administration (route not specified) of five doses of 0.025 mg/kg/day. A dose of 0.05 mg/kg/day for 28 days reduced plasma cholinesterase in three men by 35 to 40%. In other tests, each involving three to four men, doses ranging from 0.02 to 0.03 mg/kg/day produced reductions in plasma cholinesterase activity of 0, 15 to 20 and 14%. In no case was there any effect on red blood cell cholinesterase activity or on hematology, serum chemistry or urinalysis. Thus, 0.02 mg/kg/day was identified as a No-Observed-Adverse-Effect-Level (NOAEL) in humans (FAO/WHO, 1967, cited in Hayes, 1982).

Long-term Exposure

- No information was found in the available literature on the long-term health effects of diazinon in humans.

Animals

Short-term Exposure

- The acute oral toxicity of diazinon MG8 (a yellow oily liquid, 1,200 mg/mL) was studied in male albino rats (238 to 321 g) by DeProspero (1972). Four groups of six rats each were given a single dose of diazinon by gavage and then observed for 7 days. Dose levels administered were 157, 313, 625 or 1,250 mg/kg. Within 4 hours of administration, animals at the three higher levels displayed symptoms of lethargy, tremors, convulsions and runny noses. Mortality in the four groups was 0/6, 2/6, 5/6 and 6/6, respectively, with death occurring between 8 and 24 hours after exposure. At 2 days, the remaining animals at the two intermediate levels had recovered. There was no mention of adverse symptoms at the lowest dose level. Gross necropsy (performed only on animals that died) did not reveal abnormal findings. The acute oral LD_{50} value was calculated to be 395.6 mg/kg.

- Hazelette (1984) investigated the effects of dietary hypercholesteremia (HCOL) on sensitivity to diazinon in inbred male C56BL/6J mice. The LD_{50} of diazinon in HCOL mice was nearly half that of diazinon administered to normal mice (45 versus 84 mg/kg). Cholesterol feeding increased ChE activity in both blood and liver, and these increases were negated by diazinon. Hepatic diazinon levels were also higher in the HCOL animals. It was concluded that HCOL resulted in an increase in susceptibility to, and toxicity of, diazinon.

- Adult mongrel dogs (one/sex/dose) were fed diazinon (0 or 1.0 ppm in the diet) for a period of 6 weeks (Doull and Anido, 1957). Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day, this corresponds to doses of about 0 or 0.025 mg/kg/day (Lehman, 1959). Serum and erythrocyte ChE determinations were made on a weekly basis before and during exposure. Neither plasma nor red blood cell ChE varied by more than ±15% from control in exposed animals of either sex, and there were no observed changes in body weight for the test period. The apparent NOAEL for this study, based on blood chemistry parameters, is 0.025 mg/kg.

- The effect of diazinon on blood cell ChE activity was investigated in sheep after the administration of single oral doses by gavage of 50, 65, 100, 200 or 250 mg/kg (Anderson et al., 1969). Twenty-six sheep were used in the study groups. Prior to dosing, 245 untreated sheep were used to determine the normal range of erythrocyte ChE values. A typical severe clinical response consisted of profuse salivation, ataxia, dyspnea, dullness, anorexia and muscle twitching. In mild cases, only dullness and anorexia were seen, but were sufficiently pronounced to enable differentiation between normal and affected animals. Sheep that were clinically affected by diazinon

suffered a depression of ChE of more than 75%. However, there were five animals (at the 50-mg/kg dose level) that tolerated depressions of 80 to 90% without clinical effect. The ChE values fell to minimum values within 1 to 4 hours, and remained close to this level until about 8 hours after dosing, during which time symptoms were observed. In those showing maximum depressions of 80% or more, the ChE activity returned to about half its normal value by the 5th day, and thereafter recovered only very slowly during a period of several weeks.

- Davies and Holub (1980) compared the subacute toxicity of diazinon in male and female Wistar rats. The diazinon was incorporated into a semipurified diet at levels of 2 or 25 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to doses of about 0.1 or 1.2 mg/kg/day (Lehman, 1959). Effects on ChE activity were periodically assessed during a 28- to 30-day feeding period. Levels of 25 ppm (1.2 mg/kg/day) diazinon in the diet for 30 days produced more significant reduction of ChE activity in plasma (22 to 30%) and brain (5 to 9%) among treated females compared to treated males. Erythrocyte ChE activity was significantly more depressed (13 to 17%) in treated females relative to males at days 21 to 28 of the feeding period. At no time was ChE activity in any tissue more reduced among treated males than females. At the 2-ppm (0.1 mg/kg/day) dose level, diazinon failed to affect erythrocyte ChE activity in either sex relative to controls. Plasma ChE activities of treated males were not significantly different from control values, but treated females showed significant depression (29%) of plasma ChE activity. This investigation indicated that the female rat is more sensitive to the toxicity of dietary diazinon than the male. Based on the inhibition of ChE in the female animals observed at 2 ppm, the Lowest-Observed-Adverse-Effect-Level (LOAEL) for this study was identified as 0.1 mg/kg/day.

Dermal/Ocular Effects

- Nitka and Palanker (1980) investigated the primary dermal irritation and primary ocular irritation characteristics of a commercial formulation of diazinon in New Zealand White rabbits. The percentage of diazinon in the formulation was not given. After administration of a single application of 0.5 mL to abraded and intact skin of six rabbits, the formulation was judged not to be a primary dermal irritant. Nine rabbits were used to examine the effect of administration of a single dose of 0.1 mL of the formulation in one eye, and the results indicated that it was not an ocular irritant.

Long-term Exposure

- Female Wistar rats were fed a semipurified diet containing 0 or 0.1 to 15 ppm diazinon for up to 92 days with no visible toxic effects (Davies and Holub, 1980). Weight gain and food consumption were comparable to controls. Feeding studies up to 90 days revealed that rats were highly sensitive to diazinon after 31 to 35 days of exposure, as judged by reduction in plasma and erythrocyte cholinesterase (ChE) activities. ChE was judged most sensitive. A NOAEL of 0.1 ppm,

which the authors translated to an equivalent daily intake of 9 ug/kg/day, is based on plasma ChE inhibition noted for up to 35 days of feeding. Other data in this reference indicate that the depression of plasma ChE is not further inhibited by continued dosing (up to 90 days).

- Barnett and Kung (1980) fed Charles River CD-1 mice diazinon in the diet at levels of 0, 4, 20 or 100 ppm for 18 months (males) or 19 months (females). Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, this corresponds to doses of about 0, 0.6, 3 or 15 mg/kg/day (Lehman, 1959). Groups of 60 animals of each sex were used at each treatment level, and a similar group served as controls. In males, there was a significant reduction in weight gain at the highest dose. Weight reduction was significant in all female groups, although it did not appear to be dose- or treatment related. There were no significant trends in mortality. Animals showed skin irritation, loss of hair, skin lesions and piloerection. Gross and microscopic examinations showed no inflammatory, degenerative, proliferative or neoplastic lesions due to the administration of diazinon. A LOAEL of 4 ppm (0.6 mg/kg/day) was identified for the mouse in this study.

- Horn (1955) fed diazinon to groups of 20 male and 20 female rats at 0, 10, 100 or 1,000 ppm in the diet for 104 weeks. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to dose levels of about 0, 0.5, 5 or 50 mg/kg/day (Lehman, 1959). The rats were started on the diet as weanlings weighing 62 to 63 g. In preliminary studies, the highest dose caused significant growth retardation. The animals for this group were initially given 100 ppm diazinon, which was increased gradually over a period of 11 weeks to the 1,000-ppm level. Mortality occurred in all groups, including the controls, and pneumonia was common. In all groups, body weight and food consumption were comparable to the controls. Hematocrit values for males at 1,000 ppm were significantly depressed when compared to controls. At 10 ppm, plasma ChE was inhibited by 60 to 73%, red blood cell ChE was inhibited 24 to 42% and brain ChE was inhibited 8 to 10%. At 100 or 1,000 ppm, there was 95 to 100% inhibition of ChE in plasma and blood cells. At 100 ppm, brain ChE was inhibited 19 (males) to 53% (females), and this increased to 41 (males) to 59% (females) at 1,000 ppm. There were no significant gross pathological findings. Based on inhibition of blood and plasma ChE, the LOAEL for this study was identified as 10 ppm (0.5 mg/kg/day).

- Woodard et al. (1965) exposed monkeys (three/sex/dose) to diazinon orally for 52 weeks. The animals were started at doses of 0.1, 1.0 or 10 mg/kg/day for the first 35 days, but these doses were lowered to 0.05, 0.5 or 5.0 mg/kg/day for the remainder of the study, apparently because of poor food consumption and decreased weight gain. During the 52 weeks, body weight gain was slightly depressed in all treated groups, and soft stools were observed in all animals, with diarrhea in three animals (dose not specified). One female at the 0.5-mg/kg dose level had significant weight loss and signs of dehydration, emaciation, pale skin coloration and an unthrifty hair coat.

One female at this level (it is not clear whether it is the same animal just mentioned) exhibited decreased hemoglobin and a rapid sedimentation rate at 39 and 53 weeks. Plasma ChE was inhibited 93% at the high dose and 23% at the mid-dose, but no inhibition was noted at 0.05 mg/kg (the low dose). Red blood cell ChE was inhibited 90%, 0% and 0% at the high, mid and low doses, respectively. Other biochemical parameters were normal. Based on inhibition of ChE, a NOAEL of 0.05 mg/kg/day and a LOAEL of 0.5 mg/kg/day were identified in this study.

Reproductive Effects

- Johnson and Cronin (1965) conducted a three-generation reproduction study in Charles River rats. Beginning 70 days before mating, groups of 20 females were fed diazinon (as 50% wettable powder) in the diet at 4 or 8 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to doses of about 0.2 or 0.4 mg/kg/day (Lehman, 1959). The end points monitored included: general maternal condition, number of live and dead fetuses, number of pups per litter, mean pup and litter weights, gross pathology of F_{1a}, F_{2a} and F_{3a} animals, and histopathology of F_{3b} animals. All findings were reported to be normal, but there were no detailed data provided. A NOAEL of 8 ppm (0.4 mg/kg/day), the highest dose tested, was identified in this study.

- Diazinon was administered orally at dose levels of 0, 7, 25 or 100 mg/kg to groups of 18 to 22 New Zealand White rabbits on days 6 to 18 of gestation (Harris et al., 1981). At the 100-mg/kg level, 9/22 animals died. This was not quite significant ($p < 0.07$) using the Fisher Exact Test, although it was thought to be biologically significant by the authors. Of these nine animals, seven showed lesions indicative of gastrointestinal toxicity. At this dose, animals also were observed to have tremors and convulsions and were anorexic and hypoactive. These symptoms were not observed in animals at the 7- and 25-mg/kg levels. One rabbit at the 25-mg/kg level aborted on day 27, and all fetuses were dead. At this dose there were no significant changes in weight gain compared to the control, and no changes in the corpora lutea. There were also no statistically significant changes in implantation sites, proportion of live, dead or resorbed fetuses per litter, fetal weights or sex ratios. Based on these data, the NOAEL for reproductive effects for the rabbit was identified as 7 mg/kg/day.

Developmental Effects

- Diazinon at dose levels of 7, 25 or 100 mg/kg was administered orally to New Zealand White rabbits on days 6 to 18 of gestation (Harris et al., 1981). Groups of 18 to 22 rabbits, 4 to 5 months of age and weighing 3.0 to 4.1 kg, were given diazinon in 0.2% sodium carboxymethyl cellulose (CMC) and a group of controls was given 0.2% CMC only. At the 100-mg/kg level, 9/22 animals died, and although this mortality was not quite significant ($p < 0.07$) using the Fisher Exact Test, it was thought to be biologically significant by the authors.

There were no significant differences in abnormalities between the control and treated groups, and it was concluded that diazinon was neither fetotoxic nor teratogenic in the rabbit at these dose levels. With respect to fetal effects, a NOAEL of 100 mg/kg/day, the highest dose tested was identified. Based on maternal toxicity, a NOAEL of 25 mg/kg/day is identified.

- Tauchi et al. (1979) administered diazinon by gavage to groups of 30 pregnant rats for 11 days (days 7 to 17 of gestation), at dose levels of 0, 0.53, 1.45 or 4.0 mg/kg/day. In each group, 20 animals were delivered by Cesarean section on day 17, while the remaining 10 were allowed to deliver normally. There were no effects on behavior or learning ability, and no pathological lesions were detected at 10 weeks. It was concluded that diazinon was not teratogenic at the doses tested. The NOAEL for fetal effects in this study was 4.0 mg/kg/day, the highest dose tested.

Mutagenicity

- Fritz (1975) conducted a dominant lethal study in NMRI-derived albino mice. Single doses of diazinon were administered orally to males at levels of 15 or 45 mg/kg. After exposure, the males were mated to untreated females several times over a period of 6 weeks. There were no significant differences in mating ratios, the number of implantations or embryonic deaths (resorptions), and no adverse effects were observed in the progeny at either dose level. It was concluded that diazinon did not produce dominant lethal mutations in this test at the doses used.

- The mutagenicity of diazinon was tested in bacterial reversion-assay systems with five strains of Salmonella typhimurium and one strain of Escherichia coli (Moriya et al., 1983). No evidence of mutagenic activity was noted in any of the test systems.

- Four strains of Salmonella typhimurium were used to assay the mutagenic potential of diazinon (Marshall et al., 1976). Negative results were found by these investigators as well.

Carcinogenicity

- A chronic bioassay for possible carcinogenicity of diazinon was conducted in F-344 rats and B6C3F_1 mice (NCI, 1979). Groups of 50 animals were fed diazinon in the diet at the following levels: rats, 400 or 800 ppm; mice, 100 or 200 ppm. Assuming that 1 ppm in the diet of rats and mice is equivalent to 0.05 and 0.15 mg/kg/day, respectively, this corresponds to doses of about 20 or 40 mg/kg/day in rats and about 15 or 30 mg/kg/day in mice (Lehman, 1959). There was some hyperactivity noted in animals of both species, but there was no significant effect on either weight gain or mortality. There was no incidence of tumors that could be clearly related to diazinon, and it was concluded that diazinon was not carcinogenic in either species.

- Charles River CD-1 mice were fed diazinon in the diet at levels of 4, 20 or 100 ppm for 18 months (males) or 19 months (females) (Barnett and Kung, 1980). Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, this corresponds to doses of about 0.6, 3 or 15 mg/kg/day (Lehman, 1959). Groups of 60 animals of each sex were used at each treatment level, and a similar group served as controls. In males at the highest dose level there was a significant difference in weight gain from the controls. Weight reduction was significant in all female treatment groups, but it did not appear to be dose- or treatment-related. There were no significant trends in mortality. Gross and microscopic examinations showed no inflammatory, degenerative, proliferative or neoplastic lesions due to the administration of diazinon, and the study was judged to be negative with respect to carcinogenicity.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (0.02 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The most sensitive indicator of the effects of diazinon is inhibition of ChE. However, this effect is reversible, and significant inhibition of this enzyme often occurs without production of clinically significant effects.

Consequently, selection of a NOAEL or LOAEL value based only on inhibition of ChE, in the absence of any other toxic signs, is a highly conservative approach.

The study in humans described by Hayes (1982) has been selected to serve as the basis for determination of the Ten-day HA value for diazinon. Although this study is a secondary source, it establishes a NOAEL in humans based on the most sensitive end point, i.e., ChE. Hayes reported that in human volunteers, short-term exposure to doses of 0.02 mg/kg/day did not result in decreased ChE levels, while doses of 0.025 to 0.05 mg/kg/day caused ChE reductions of 15 to 40%. This NOAEL (0.02 mg/kg/day) is supported by studies in animals; e.g., based on blood and serum ChE, Doull and Anido (1957) reported a NOAEL of 0.05 mg/kg/day in a 6-week study in dogs.

Using a NOAEL of 0.02 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.02 \text{ mg/kg/day})\ (10 \text{ kg})}{(10)\ (1 \text{ L/day})} = 0.02 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.02 mg/kg/day = NOAEL, based on absence of ChE inhibition in humans.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The study by Woodard et al. (1965) has been selected to serve as the basis for the Longer-term HA. Based on inhibition of plasma ChE in monkeys exposed for 52 weeks, this study identified a NOAEL of 0.05 and a LOAEL of 0.5 mg/kg/day. These values are supported by the NOAEL for ChE inhibition of 0.025 mg/kg/day identified in a 6-week feeding study in dogs (Doull and Anido, 1957) and by the LOAEL of 0.5 mg/kg/day identified by Horn (1955), based on ChE inhibition in rats exposed for 2 years.

Using a NOAEL of 0.05 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.005 \text{ mg/L } (5.0 \text{ ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of ChE inhibition in monkeys given diazinon orally for 52 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 0.05 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.05 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.0175 \text{ mg/L } (17.5 \text{ ug/L})$$

where:

0.05 mg/kg/day = NOAEL, based on absence of ChE inhibition in monkeys given diazinon orally for 52 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Available lifetime studies were not judged adequate for use in the determination of the Lifetime HAs since toxicological end points and numbers of

animals tested were limited. Therefore, the 13-week study of Davies and Holub (1980) has been selected to serve as the basis for determination of the Lifetime HA, with an additional safety factor of 10 for studies of less than a lifetime. This study identified a NOAEL of 0.009 mg/kg/day.

Using a NOAEL of 0.009 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.009 \text{ mg/kg/day})}{(100)} = 0.00009 \text{ mg/kg/day}$$

where:

0.009 mg/kg/day = NOAEL, based on plasma cholinesterase inhibition in rats exposed to diazinon in the diet for up to 92 days.

100 = uncertainty factor of 10 for the end point of toxicity-cholinesterase inhibition and an additional factor of 10 for a study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.00009 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.00315 \text{ mg/L } (3.15 \text{ ug/L})$$

where:

0.00009 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.00315 mg/L) (20%) = 0.00063 mg/L (0.63 ug/L)

where:

0.00315 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Two studies on the carcinogenicity of diazinon in mice have been reported (NCI, 1979; Barnett and Kung, 1980). Neither study revealed any evidence of carcinogenicity.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of diazinon.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), diazinon may be classified in Group E: evidence of non-carcinogenicity for humans. This category is for substances that show no evidence of carcinogenicity in at least two adequate animal tests or in both epidemiologic and animal studies.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1977) has calculated an ADI of 0.002 mg/kg/day, based on a NOAEL in humans of 0.02 mg/kg/day and an uncertainty factor of 10. Assuming average body weight of human adult of 70 kg, daily consumption of 2 liters of water and a 20% contribution from water, NAS (1977) calculated a Suggested-No-Adverse-Effect-Level of 0.014 mg/L.

VII. ANALYTICAL METHODS

- Analysis of diazinon is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using a capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for diazinon but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that reverse osmosis (RO), granular-activated carbon (GAC) adsorption and ozonation will remove diazinon from water. The percent removal efficiency ranged from 75 to 100%.

- Laboratory studies indicate that RO is a promising treatment method for diazinion-contaminated waters. Chian (1975) reported 100% removal efficiency using a cross-linked polyethylenimine (NS-100) membrane and 99.88% removal efficiency with a cellulose acetate (CA) membrane. Both membranes operated separately at 600 psi and a flux rate of 8-12 gal/ft^2/day. Membrane adsorption, however, is a major concern and must be considered as breakthrough of diazinon would probably occur once the adsorption potential of the membrane was exhausted.

- GAC is effective for diazinon removal. Dennis and Kobylinski (1983) and Dennis et al. (1983) reported 94.5%, 90.5% and 76% diazinon removal efficiency from wastewater in 6 hr. treatment periods with 45 lbs of GAC. Also, 95% diazinon removal efficiency was achieved in an 8-hr. treatment period with 40 lbs of GAC.

- Whittaker (1980) experimentally determined GAC adsorption isotherms for diazinon and diazinon-methyl parathion solutions in distilled water indicate that treatment with GAC can be used to remove diazinon.

- UV/03 oxidation treatment appears to be an effective diazinon removal method. UV/03 oxidized 75% of diazinon at 3.4 gm/L ozone dosage and a retention time of 204 minutes. When lime pretreatment was used, UV/03 oxidized 99+% of diazinon at 4.1 gm/L ozone dosage and 240 minutes retention time (Zeff et al., 1984).

- Some treatment technologies for the removal of diazinon from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt diazinon removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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